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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application]This invention relates to the whitening agent which has the whitening effect of the skin.
[0002]
[Description of the Prior Art]It is thought that the activity of a tyrosinase rises, melanin generates developmental mechanisms, such as a stain of the skin and a freckle, and this carries out unusual deposition into the skin by operation of melanocyte-stimulating hormone, ultraviolet rays, etc.
[0003]The request to the whitening agent which makes normal skin color recover the acquired unusual self-possessed part of melanin, such as a stain and a freckle, where melanin carries out unusual deposition, and which is made in the skin is high, and many drugs are developed, and it is commercialized.
[0004]For example, a method of prescribing for the patient the vitamin C (L-ascorbic acid) which has reduction ability in large quantities, The method of making the method and vitamin C which use peroxides, such as a method of injecting glutathione, hydrogen peroxide which has a bleaching action of melanin, zinc peroxide, and sodium peroxide, for a part, cystein, etc. the gestalt of ointment, cream, a lotion, etc., and applying to a part, etc. are taken.
[0005]The hydroquinone agent is used as drugs in Europe and America [A. B. Lerner and Fitzpatrick, Biochemistry of Melanin formation, 30, 91 (1950)].
[0006]
[Problem(s) to be Solved by the Invention]In the above-mentioned conventional whitening agent, in the system containing moisture, vitamin C is unstable, it is easy to cause a stench and discoloration, and thiol system compounds, such as glutathione and cystein, have slow whitening actions, and the effect is insufficient.

[0007]this invention person examined the whitening agent which has the operation which checks the activity of the tyrosinase related to the developmental mechanism of melanin, checks having the operation the specific resorcinol derivative excelled [operation] in the activity inhibition effect of the tyrosinase, and came to complete this invention.
[0008]
[Means for Solving the Problem]This invention consists of a whitening agent containing 4-n-butyl resorcinol or 4-isoamylresorcinol.
[0009]4-n-butyl resorcinol or 4-isoamylresorcinol used for a whitening agent of this invention which consists of said composition is a publicly known compound, For example, saturated carboxylic acid and output which made resorcinol condense under existence of zinc chloride, How to return with zinc amalgam/chloride (Lille. J. Bitter and LA. Peiner. V, Tr. Nauch-Issled.Inst. slantsev 1969, No.18,127), Or it is easily obtained by a method (the British patent No. 1581428 specification) etc. to which resorcinol, n-butyl alcohol, or isoamyl alcohol is made to react under a 200-400 ** elevated temperature using an alumina catalyst.
[0010]In a whitening agent of this invention, 4-n-butyl resorcinol or 4-isoamylresorcinol is used with the usual cosmetics base.
[0011]4-n-butyl resorcinol or 4-isoamylresorcinol should just be blended at about 0.01 to 15.0 % of the weight in a whitening agent, and is especially blended at about 0.1 to 10.0 % of the weight preferably.
[0012]As a cosmetics base, what is carrying out normal use to whitening cosmetics can be used as it is, for example, it can use with gestalten, such as cream, ointment, a milky lotion, face toilet, oil, and a packing agent.
[0013]As a cream base, yellow bees wax, cetyl alcohol, stearic acid, glycerin, propylene glycol, propylene glycol monostearate, polyoxyethylene cetyl ether, etc. can be used, for example.
[0014]As a face toilet base, oleyl alcohol, ethanol, propylene glycol, glycerin, lauryl ether, sorbitan mono- laurate ester, etc. can be used, for example.
[0015]The whitening agent of this invention can add various kinds of medicinal properties, such as an ultraviolet ray absorbent, allantoin, and a placenta extract, a thickener, calamine, paints, an anti-oxidant, a chelating agent, perfume, etc. to the above-mentioned cosmetics base if needed.
[0016]
[Example]Hereafter, the concrete composition of the whitening agent of this invention is explained based on an example.
[0017]The example 1 (manufacture of 4-n-butyl resorcinol) of manufacture
After 71.85 g of thionyl chlorides were dropped at the butanoic acid 17.6g over 1 hour at the room temperature, it agitated for further 5 hours. After ending reaction, the superfluous thionyl chloride was distilled off and the residue was obtained.

[0018]Subsequently, after returning to a room temperature, it was made to react for further 8 hours, after taught and adding 26.42 g of resorcinol to the suspension of 150 ml of methylene chlorides and the zinc chloride 81.77g which cooled this residue at 10 ** continuously and making it react for 30 minutes.

[0019]Add 100 ml of HCl(s) 5% to this reaction mixture, and 100 ml of isopropyl ether extracts twice, After distilling off isopropyl ether furthermore, it refined having covered the residue over column chromatography (silica gel, n-hexane/ethyl acetate: 3/1 (capacity factor)), and n-butyryl resorcinol was obtained.

[0020]Then, the decantation was carried out and solution was thrown away, after shaking the zinc dust 30.0g for 5 minutes with the mercuric chloride 2.50g, 1.5 ml of concentrated hydrochloric acid, and 38 ml of water. To this, 20 ml of water, 45 ml of concentrated hydrochloric acid, 25 ml of toluene, and 13.3 g of previous n-butyryl resorcinol were added one by one, and heating flowing back was carried out for 30 hours. In order to maintain the concentration of acid in the meantime, 12.5 ml of concentrated hydrochloric acid was added 4 times every 6 hours.

[0021]After cooling and separating liquids to a room temperature, 50 ml of isopropyl ether extracted the water layer 3 times, and it doubled with the organic layer, and rinsed with 100 ml of water.

[0022]8.1 g of n-butyl resorcinol of the colorless needle crystal was obtained by distilling off a solvent by an evaporator after an appropriate time, and crystallizing a residue from n-hexane after an appropriate time.

[0023]The example 2 (manufacture of 4-isoamylresorcinol) of manufacture

After 71.85 g of thionyl chlorides were dropped at the isovaleric acid 20.4g over 1 hour at the room temperature, it agitated for further 5 hours. After ending reaction, the superfluous thionyl chloride was distilled off and the residue was obtained.

[0024]Subsequently, after returning to a room temperature, it was made to react for further 8 hours, after taught and adding 26.42 g of resorcinol to the suspension of 150 ml of methylene chlorides and the zinc chloride 81.77g which cooled this residue at 10 ** continuously and making it react for 30 minutes.

[0025]Add 100 ml of HCl(s) 5% to this reaction mixture, and 100 ml of isopropyl ether extracts twice, After distilling off isopropyl ether furthermore, it refined having covered the residue over column chromatography (silica gel, n-hexane/ethyl acetate: 3/1 (capacity factor)), and isovaleryl resorcinol was obtained.

[0026]Then, the decantation was carried out and solution was thrown away, after shaking the zinc dust 30.0g for 5 minutes with the mercuric chloride 2.50g, 1.5 ml of concentrated hydrochloric acid, and 38 ml of water. To this, 20 ml of water, 45 ml of concentrated hydrochloric acid, 25 ml of toluene, and 14.6 g of previous isovaleryl resorcinol were added

one by one, and heating flowing back was carried out for 30 hours. In order to maintain the concentration of acid in the meantime, 12.5 ml of concentrated hydrochloric acid was added 4 times every 6 hours.

[0027]After cooling and separating liquids to a room temperature, 50 ml of isopropyl ether extracted the water layer 3 times, and it doubled with the organic layer, and rinsed with 100 ml of water.

[0028]6.5 g of isoamylresorcinol of the colorless needle crystal was obtained by distilling off a solvent by an evaporator after an appropriate time, and crystallizing a residue from n-hexane after an appropriate time.

[0029]Reference example 3 (manufacture of the resorcinol derivative for comparison)
By changing the organic acid made to react to a thionyl chloride, respectively, 4-methyl resorcinol, 4-ethyl resorcinol, 4-n-hexylresorcinol, 4-n-octyl resorcinol, and 4-n-dodecyl resorcinol were compounded like the process of the reference example 1.

[0030][Experiment 1] The 4-n-butyl resorcinol and 4-isoamylresorcinol which are used for the whitening agent of this invention prove by experiment checking effectively the activity of the tyrosinase which participates in generating of melanin.

[0031]A tyrosinase is a copper content enzyme which governs the melanin synthesis which uses tyrosine as a starting material.
It is thought that this enzyme acts as a catalyst of the generation phase of the dopa (tyrosine hydroxylase) which is an intermediate of melanin synthesis, a dopa quinone (dopa oxidase), and indole- 5,6-quinone.

[0032]In this experiment, 4-n-butyl resorcinol and 4-isoamylresorcinol measured the generation reaction of the dopa from tyrosine, and the grade which inhibits the generation reaction of a dopa quinone from dopa, and followed it as the rule of thumb of inhibition of tyrosinase activity.

[0033]As analyte, 4-methyl resorcinol, 4-ethyl resorcinol, 4-n-dodecyl resorcinol, and hydroquinone were used as analyte for 4-n-butyl resorcinol, 4-isoamylresorcinol, and comparison.

[0034](1) 3 ml of measurement substrate (L-tyrosine, $1x10^{-4}$mol) solutions of tyrosine hydroxylation activity were put into the cell of an absorptiometer, it was easy to add and 30micro of analytes l of the 100 time concentration of the last concentration were mixed.

[0035]Checked ** of ultraviolet-region absorption of a substrate or analyte, and nothing, and added tyrosinase (Mushroom, 200Unit, product made by Sigma) 50microl, the reaction was made to start, and change of the absorbance in 280 nm which is the maximal absorption of L-DOPA was measured.

[0036]Tyrosine hydroxylation activity was displayed by mol dopa/min/mg (protein). The protein

volume was measured in accordance with the method of Lowry. A result is shown in [Table 1].

[0037]

[Table 1]

被　　検　　体	活性度
コントロール	１．８３
４－ｎ－ブチルレゾルシノール	０．００
４－イソアミルレゾルシノール	０．００
４－メチルレゾルシノール	１．７８
４－エチルレゾルシノール	０．００
４－ｎ－ドデシルレゾルシノール	０．３３
ハイドロキノン	０．００

[0038](2) the dopa generated using the measurement substrate (L-DOPA, $5x10^{-3}$mol) of the degree of dopa oxidation activity -- chromium was measured with 475 nm wavelengths. It measured like measurement of tyrosine hydroxylation activity using tyrosinase 10Unit except it. the degree of dopa oxidation activity -- mumol -- dopa -- it displayed by chromium/min/mg (protein). A result is shown in [Table 2].

[0039]

[Table 2]

被　　検　　体	活　性　度
コントロール	１５．８０
４－ｎ－ブチルレゾルシノール	０．００
４－イソアミルレゾルシノール	０．００
４－メチルレゾルシノール	１６．８１
４－エチルレゾルシノール	７．４４
４－ｎ－ドデシルレゾルシノール	７．１９
ハイドロキノン	２６．９４

[0040][Experiment 2] It checked that an Ames examination was done using Salmonella typhimurium and there was no mutagen student about 4-isoamylresorcinol.
[0041][Experiment 3] Hydroquinone is used as analyte as 4-isoamylresorcinol and a comparison compound, Analyte was dissolved in the physiological saline, this was prescribed for the patient and (i. p.) administered hypodermically in internal use (p. o.) and **** to the ddy system male mouse of one groups [ten] (s. c.), and the life and death by after-administration 24 hours were observed.
[0042]Based on the result, LD_{50} was computed in accordance with the Litchfield- wilcoxom method. A result is shown in [Table 3].
[0043]
[Table 3]

被　検　体	LD_{50} (mg/kg)		
	p.o.	i.p.	s.c.
４－イソアミルレゾルシノール	＞500	268.8	＞500
ハイドロキノン	489.0	144.0	338.8

[0044][Experiment 4] 3 ml of substrate (L-tyrosine, $1x10^{-4}$mol) solutions are put into the cell of an absorptiometer, After adding 30micro of analytes l of various kinds of concentration and

mixing, change by 280 nm which is the maximal absorption of L-DOPA at the time of adding tyrosinase (Mushroom origin, 20Unit, product made by Sigma) 50microl, and making it react for 400 minutes was recorded, and the generation rate of L-DOPA was measured.

[0045]The grade of the activity inhibition operation of the tyrosinase of various kinds of analytes was judged with the concentration (IC50mol) of analyte in case the generation rate of L-DOPA from tyrosine is set to one half of the generation rates of L-DOPA from tyrosine at the time of not making analyte exist.

[0046]As analyte, use 4-n-butyl resorcinol and 4-isoamylresorcinol and as analyte for comparison, 4-methyl resorcinol, 4-ethyl resorcinol, 4-n-hexylresorcinol, 4-n-octyl resorcinol, 4-n-dodecyl resorcinol, and hydroquinone were used.

[0047]A result is shown in [Table 4].

[0048]

[Table 4]

実験No.	被　　検　　体	IC50mol
1	4－n－ブチルレゾルシノール	1.15×10^{-7}
2	4－イソアミルレゾルシノール	1.06×10^{-7}
3	4－メチルレゾルシノール	$>10^{-3}$
4	4－エチルレゾルシノール	1.69×10^{-7}
5	4－n－ヘキシルレゾルシノール	2.54×10^{-7}
6	4－n－オクチルレゾルシノール	2.59×10^{-7}
7	4－n－ドデシルレゾルシノール	3.60×10^{-6}
8	ハイドロキノン	2.68×10^{-6}

[0049]From an experimental result, the tyrosinase activity inhibitory action of 4-n-butyl resorcinol and 4-isoamylresorcinol is about 1.5 times the tyrosinase activity inhibitory action of 4-ethyl resorcinol.

It is about 2.5 times the tyrosinase activity inhibitory action of 4-n-hexylresorcinol and 4-n-octyl resorcinol, It is about 31 to 34 times the tyrosinase activity inhibitory action of 4-n-dodecyl resorcinol, and has checked that it was about 23 to 25 times the tyrosinase activity inhibitory action of hydroquinone further.

[0050]The whitening agent (lotion) by one or less-example presentation was prepared.
[0051]
Propylene glycol.....10.0 weight-section ethyl alcohol .....20.0 weight-section liquid paraffin .....2.0 weight-section polyoxyethylene (30) hydrogenated castor oil ..... 1.0 weight-section 4-isoamylresorcinol .....8.0 weight-section polyethylene glycol .....5.0 weight-section citrate .....0.2 weight-section sodium phosphate .....0.3 weight-section allantoin .....0.05 weight-section EDTA-2Na .....0.05 weight-section anti-oxidant .....0.02 weight section perfume .....0.2 weight-section purified water .....53.18 weight sections [0052]The whitening agent (cream) by two or less-example presentation was prepared.
[0053]
Hard paraffin.....2.0 weight-section stearyl alcohol .....4.0 weight-section squalane .....2.0 weight-section liquid paraffin .....6.0 weight-section glyceryl monostearate.....2.5 weight-section polyoxyethylenesorbitan monostearate .....2.5 weight-section ethyl alcohol .....9.0 weight-section propylene glycol .....8.0 weight-section 4-isoamylresorcinol .....4.0 weight-section 2-hydroxy-4-methoxybenzophenone.....3.0 weight-section hydrophobicity-ized particulate titanium oxide.....5.0 weight-section purified water .....52.5 weight sections [0054]The whitening agent (foundation) by three or less-example presentation was prepared.
[0055]
Hydrophobicity-ized particulate titanium oxide.....7.0 weight-section isostearic acid triglyceride.....2.0 weight-section 2-octyldodecyl olate .....8.0 weight-section liquid paraffin .....3.0 weight-section cetyl alcohol .....5.0 weight-section candelilla wax .....2.0 weight-section 4-isoamylresorcinol .....5.0 weight-section polyoxyethylene (25) monostearate .....2.0 weight-section sorbitan monostearate.....1.0 weight-section Synthetic Ochre .....1.3 weight-section rouge .....0.8 weight-section polyethylene glycol .....4.0 weight-section methylparaben .....0.2 weight section perfume .....0.2 weight-section purified water .....58.5 weight sections [0056]The whitening agent (powder) by four or less-example presentation was prepared.
[0057]
Talc.....80.0 weight-section crystallinity cellulose .....5.0 weight-section ultramarine .....1.0 weight-section spherical calcium silicate .....3.0 weight-section particulate titanium oxide .....3.5 weight-section 4-isoamylresorcinol .....3.0 weight-section squalane .....4.5 weight sections [0058]The whitening agent (lotion) by five or less-example presentation was prepared.
[0059]
Propylene glycol.....15.0 weight-section L-menthol .....0.1 weight-section ethanol .....15.0 weight-section polyoxyethylene (30) hydrogenated castor oil ..... 0.5 weight-section anti-

inflammatory agent .....1.0 weight-section 4-isoamylresorcinol .....1.5 weight-section iso [triethanolamine] ferulate.....3.5 weight section perfume .....0.3 weight-section purified water .....65.1 weight sections [0060]The whitening agent (oil) by six or less-example presentation was prepared.

[0061]

Squalane.....47.0 weight-section castor oil .....47.0 weight-section isoferulic acid-2-ethylhexyl .....5.0 weight-section 4-isoamylresorcinol .....0.79 weight section perfume .....0.2 weight-section anti-oxidant .....0.01 weight sections [0062]The whitening agent (lotion) by seven or less-example presentation was prepared.

[0063]

Propylene glycol.....10.0 weight-section ethyl alcohol .....20.0 weight-section liquid paraffin .....2.0 weight-section polyoxyethylene (30) hydrogenated castor oil ..... 1.0 weight-section 4-n-butyl resorcinol .....8.0 weight-section polyethylene glycol .....5.0 weight-section citrate .....0.2 weight-section sodium phosphate .....0.3 weight-section allantoin .....0.05 weight-section EDTA-2Na .....0.05 weight-section anti-oxidant .....0.02 weight section perfume .....0.2 weight-section purified water .....53.18 weight sections [0064]

[Effect of the Invention]The whitening agent of this invention contains the 4-n-butyl resorcinol or 4-isoamylresorcinol which checks effectively the activity of the tyrosinase which participates in generating of melanin.

The effect outstanding to whitening of the skin is done so.

[Translation done.]